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(54) Title: COMPOSITIONS COMPRISING A COMBINATION OF A FREE SPHINGOID BASE AND A CERAMIDE AND USES THEREOF

(57) Abstract

The present invention discloses a composition for topical use comprising a free sphingoid base and a ceramide. The compositions of the invention are suitable for application to skin conditions associated with an impaired barrier function, in particular to skin conditions further associated with a deranged regulation of cell growth and differentiation, an inflammatory condition and/or an infectious state.

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Compositions comprising a combination of a free sphingoid base and a ceramide and uses thereof

Field of the invention

The present invention relates to the field of topical use of compositions comprising a selected combination of sphingolipids.

Background of the invention

The human skin forms a structural and adapted barrier to the environment. It further plays an important physiological role since it provides not only protection and thermoregulation, but also has a metabolic and sensorial function and storage capacity.

It has been shown that the lipid composition of the epidermal cells within the skin changes considerably when the cells migrate to the outer surface and differentiate. The cells in the basal layer contain a complex lipid composition, with phospholipids as the major constituent. In the granular layer the phospholipid content is diminished while the amount of cerebrosides (glycosylceramides), ceramides, cholesterol and cholestorol sulphate is increased as result of *de novo* synthesis and storage into the so-called lamellar bodies. In the outermost lipid layer of the epidermis, called the stratum corneum (horny layer) the phospholipids and cerebrosides have vanished completely. The most abundant lipids in this layer are ceramides, which mainly have been formed by enzymatic deglycosylation of cerebrosides.

The barrier function of the skin mainly is provided by the stratum corneum. The stratum corneum consists of corneocytes embedded in an extracellular matrix of multiple bilayers of lipids. The intercellular lipid phase of the stratum corneum has roughly the following composition: 40% ceramides, 25% cholesterol, 10% cholesteryl sulphate and 25% free fatty acids. As long as the "bricks and mortar"

construction of the stratum corneum is not affected, the skin is provided with both a perfect protective layer and a filter-active permeability layer.

Several categories of skin conditions or disorders are known which are characterized by an impaired lipid barrier function, further accompanied by characteristics like a deranged regulation of cell growth and differentiation (e.g. hyperproliferation and/or decreased differentiation of keratinocytes, decreased desquamation of corneocytes), an imflammatory response and/or an infectious state. In these skin conditions, the skin generally displays a rough, red, dry, chapped and/or swollen character. Typical examples of such disorders are xerosis, acne vulgaris, psoriasis, atopic dermatitis, contact dermatitis, UV-induced erythema, and the like.

Satisfactory treatment methods for these disorders presently are not available. Emollient creams and lotions may relieve part of the symptoms, but often only temporarily. Conventional antiimflammatory creams, of which corticosteroid creams form the main part, are more effective for the treatment of certain disorders but continued use may reduce the effectiveness of the treatment and/or may give side reactions. In addition, conventional antiinflammatory as well as antimicrobial creams typically are not adapted to restore an impaired barrier function.

Ceramides are generally applied in cosmetics because of their moisture-retaining properties (see for instance Japanese patent application J61-260008).

In International patent application WO94/00127 it has been described that formulations containing specific lipid mixtures should be applied for an optimal treatment of skin disorders associated with a disrupted epidermal barrier. Said lipid mixtures comprise lipids selected from the three major classes of naturally-occurring epidermal lipids, i.e. the classes of ceramides, cholesterol and free fatty acids. However, in order to be optimally effective for skin conditions associated with inflammatory or infectious phenomena, these formulations have to be applied together with conventionally used therapeutic agents.

Surprisingly, it is shown by the present invention that topical compositions comprising a combination of a free sphingoid base and a ceramide have a beneficial effect when applied on skin conditions associated with an impaired barrier function, and especially when applied on skin conditions further associated with a deranged regulation of cell growth and differentiation, inflammatory and/or infectious phenomena.

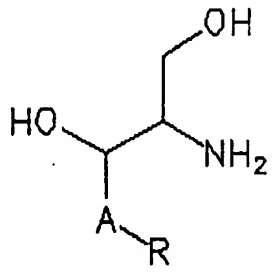
Description of the invention

The present invention discloses compositions suitable for topical use comprising a combination of a free sphingoid base and a ceramide. The topical compositions of the invention can be cosmetic as well as dermatologic compositions.

It is shown by the present invention that topical compositions comprising a combination of a free sphingoid base and a ceramide have a positive and beneficial effect on skin conditions associated with an impaired lipid barrier function. The synergistic effects of the combination of a free sphingoid base and a ceramide become even more apparent when the compositions according to the invention are used for the treatment of skin conditions wherein an impaired lipid barrier function further is associated with a deranged regulation of cell growth and differentiation, an imflammatory condition and/or an infectious state. Said deranged regulation of cell growth and differentiation is characterized by conditions like hyperproliferation of keratinocytes, decreased differentiation of keratinocytes and/or decreased desquamation of corneocytes.

The present invention shows that the presence of a free sphingoid base especially improves the efficacy of the composition of the invention with regard to its antiinflammatory and/or its antimicrobial activity. It is shown that this efficacy improvement is due to, in particular, an antimicrobial and antiinflammatory activity of the free sphingoid base.

The free sphingoid base present in the composition according to the invention has a general structure according to Formula 1:



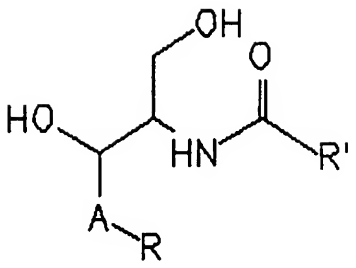
(1)

wherein:

A is CH_2-CH_2, CH=CH or C(H)OH-CH_2, and

R is a straight chain or branched alkyl group having 10 to 22 carbon atoms which may optionally contain one or more double bonds and/or may optionally be substituted with one or more hydroxyl groups, preferably is a straight chain alkyl group having 12 to 18 carbon atoms, more preferably is a straight chain alkyl group having 13 carbon atoms.

The ceramide present in the composition according to the invention has a general structure according to Formula 2:



(2)

wherein:

A and R are defined as above, and

R' is a straight chain or branched alkyl group having 13 to 55 carbon atoms, preferably 15 to 50 carbon atoms, more preferably 17 to 44 carbon atoms; the alkyl chain may optionally be interrupted by an oxygen atom or by an internal ester group; may optionally contain one or more double bonds; and may optionally be substituted with one or more hydroxyl groups.

The free sphingoid base which is present in the composition of the invention preferably is a sphingosine, a sphinganine or a phytosphingosine. More preferably, the free sphingoid base is a phytosphingosine obtainable by deacetylation of tetraacetylphytosphingosine obtainable by fermentation of the yeast *Pichia ciferri*.

The ceramide which is present in the composition of the invention can be extracted from a natural source, for instance a mammalian source, or can be obtained via synthetic means. An example of a suitable chemical synthesis method is the acylation of a free sphingoid base with a suitable fatty acid, for instance via the acylation method as disclosed in international patent application WO93/20038.

In a preferred embodiment of the invention, the ceramide present in the composition of the invention is a ceramide which corresponds in stereochemical configuration to a ceramide isolatable from mammalian skin. Ceramides as isolated from mammalian skin typically can be subdivided in six heterogeneous classes of compounds, ceramide 1, 2, 3, 4, 5, 6I and 6II. In general, these ceramides consist of a free

sphingoid base in amide linkage with a nonhydroxy or an α-hydroxy fatty acid, or an ω-hydroxy fatty acid esterified with an additional fatty acid. A ceramide which corresponds in stereochemical configuration to a mammalian skin ceramide may for instance be obtained by acylation of *Pichia ciferri*-derived phytosphingosine. Examples of such ceramides are the ceramides disclosed in international patent applications WO93/20038, WO95/11881, WO95/25716 and WO96/10557.

Within the context of the present invention, an individual ceramide as well as a mixture of two or more different ceramides can be applied in a topical composition.

In that regard, said mixture of two or more different ceramides may include various ceramide combinations, the choice of a specific combination depending among others on the desired application.

A combination of two or more representatives of each ceramide class may for instance be applied, since said combination may lead to an increased ceramide solubility in the composition according to the invention. Individual ceramides may tend to crystallize and consequently become inert and unfunctional.

A further option is a combination of, on the one hand, a sphinganine- and/or sphingosine-containing ceramide and, on the other hand, a phytosphingosine-containing ceramide (e.g. ceramide 1 and/or 2 and/or 4/5 with ceramide 3 and/or Ceramide 6). Such a combination consists of two types of ceramides having a head group which differs in hydrophilicity and this may increase barrier enhancing properties of the same.

For the same reason, a combination is feasible of a ceramide containing an α-hydroxy fatty acid with a ceramide containing a non-hydroxylated fatty acid (e.g. ceramide 1 and/or ceramide 2 and/or ceramide 3 with ceramide 4/5 and/or ceramide 6).

Further feasible is a combination of a ceramide containing a medium chain fatty acyl group of 16 to 22 carbon atoms with a ceramide containing a long chain fatty acyl groups of 22 to 32 carbon atoms, since such a combination naturally occurs in the stratum corneum and may

also be important for a stronger barrier structure (Bouwstra *et al.* (1996), J. Lipid Res. 37, 999-1011).

The composition of the invention optionally may comprise one or more additional skin lipid compounds, such as cholesterol, cholesterol esters like cholesteryl sulphate, free fatty acids like palmitic, stearic, behenic, oleic and/or linoleic acid and/or other sphingolipids like glycoceramides. The composition of the invention may further comprise ceramide compounds having a short-chain acyl group, said short chain acyl group optionally being α-hydroxylated (so-called short-chain ceramides).

With respect to glycoceramides, two groups of these compounds are typically distinguished, i.e. cerebrosides and gangliosides. A cerebroside is understood to be a glycoceramide wherein a monosaccharide, mostly glucose or galactose, is attached to the oxygen of the $-CH_2OH$ group of the ceramide according to Formula 2. In gangliosides oligosaccharides, frequently including sialic acid, are attached to the same.

With respect to short-chain ceramides, a short chain acyl group is meant to comprise acyl groups having 2 to 14 carbon atoms. A preferred ceramide with a short-chain acyl group is acetylphytosphingosine. Examples of ceramides having a short-chain α-hydroxyacyl group are disclosed in international patent application WO95/29151.

In one embodiment of the invention, a composition comprising a free sphingoid base and a ceramide may contain as the sole type of ceramide compound a glycoceramide or a short-chain ceramide. In another embodiment, the ceramide compound in the composition of the invention may be a mixture of a glycoceramide and a short-chain ceramide.

Next to the free sphingoid base and the ceramide, other active ingredients may be present in the composition according to the invention. For instance, the combination of a free sphingoid base and a ceramide may advantageously be applied in combination with a conventional antiinflammatory and/or antimicrobial agent, where said conventional antiinflammatory and/or antimicrobial agent may be applied

in substantially lower concentrations than typically used, because of the activity of the free sphingoid base.

An example of a conventionally used antiinflammatory agent is a corticosteroid.

Other active ingredients which may advantageously be applied in the compositions according to the invention, in combination with a free sphingoid base and a ceramide, are agents which have an effect on skin appearance.

For instance, yeast β-glucan may be applied in the composition according to the invention to reduce UV-induced erythema. Skin-peeling agents, like α-hydroxyacids, urea, salicylic acid or proteases, may be applied in the composition according to the invention to improve desquamation and/or decrease roughness of the skin. Retinoids may be applied in the composition according to the invention to stimulate the mitotic and metabolic activity of epidermal cells. Vitamin C and/or E may be applied in the composition of the invention for their antioxidant activity on skin components, which favours their application as, for instance, antiageing agents.

The free sphingoid base as well as the ceramide may be present in the composition according to the invention in a concentration of 0.001 to 10%, preferably in a concentration of 0.005 to 5%, more preferably in a concentration of 0.01-2%, most preferably in a concentration of 0.02-1.0%.

The ratio of free sphingoid base to ceramide in the composition according to the invention may lie within a range of 1 to 10 to 10 to 1. Preferably, said ratio may vary from about 1 to 5 to about 5 to 1. More preferably, said ratio may vary from about 1 to 5 to about 1 to 1.

Next to the active ingredients, the topical preparations of the invention further include the usual components.

The composition comprises a vehicle to enable the active ingredients to be conveyed to the skin.

The vehicle enables proper application on skin and/or hair, to provide both a dermatological as well as a cosmetic treatment. The composition may comprise a solid, semi-solid or liquid cosmetically and/or physiologically acceptable

vehicle. The nature of the vehicle will depend upon the method chosen for topical administration of the composition. Vehicles other than water can include liquid or solid emollients, solvents, humectants, thickeners, powders, surfactants, which are also sometimes designated as emulsifiers, solubilizers, propellants and other active ingredients.

Emollients can be classified under such general chemical categories as (fatty acid)esters, fatty acids, (fatty)alcohols, polyols, (natural) waxes, natural oils, silicone oils, both volatile and non-volatile and hydrocarbons such as mineral oil, petroleum jelly, vaseline, squalens and (iso)paraffin.

Surfactants including emulsifiers may be cationic, nonionic, anionic or amphoteric in nature. A single type of surfactant and/or combinations of surfactants may be employed.

Illustrative for nonionic surfactants are alkoxylated compounds based upon fatty alcohols, fatty acids and sorbitan.

Anionic-type surfactants may include fatty acid soaps, lauryl sulphate salts, lauryl ether sulphate salts, alkyl benzene sulphonates, alkyl acid phosphates.

Amphoteric surfactants include materials as dialkylamine oxide and various types of betaines, such as cocoamido propyl betaine.

Cationic surfactants comprise quaternary ammonium compounds (Quats) such as cetyl trimethyl ammonium chloride or bromide.

A special class of surfactants are silicone surfactants, which are high molecular weight polymers of dimethyl polysiloxane with polyoxyethylene and/or polyoxypropylene side chains having a molecular weight of 10.000 to 50.000 D.

In general, surfactants used for the preparation of emulsions include emulsifiers comprising compounds having a HLB (hydrophilic/lipophilic balance) value which is in the lower as well as in the higher ranges, i.e. compounds which are able to form a water-in-oil as well as compounds which are able to form an oil-in-water emulsion, respectively.

Typically, if a water-in-oil emulsion is required, the HLB value of the emulsifier or mixture of emulsifiers varies between about 1 and 7. For an oil-in-water emulsion, said HLB value is higher than about 7.

Specific emulsifiers comprise emulsifiers which are able to form a lamellar phase (liquid crystalline or gel phase). Lamellar phases are formed at the oil-water interphase of an oil-in-water emulsion and directly incorporate the free sphingoid base and the ceramide. Examples of such specific emulsifiers are:

1. Fatty acids + neutralized fatty acids:
- e.g. stearic acid, isostearic acid, etc.

2. Glyceryl mono-fatty acid ester + neutralized fatty acids:
- glyceryl stearate SE, glyceryl oleate SE

3. Glyceryl mono-fatty acid ester + ethoxylated fatty alcohols/esters:
- glyceryl stearate + Ceteareth-20 + various
- glyceryl stearate + PEG-20 glyceryl stearate

4. High-ethoxylated fatty alcohols + low-ethoxylated fatty alcohols (+ polar emollients):
- Steareth-2 + Steareth-21 (+ PPG-15 stearyl ether/fatty alcohol)
- Ceteareth-6 + Ceteareth-25
- Cetearyl Alcohol + Ceteareth-20

5. Various polyglyceryl esters + combinations:
- polyglyceryl-3-methyl glucose distearate.
- polyglyceryl-10 pentastearate + behenyl alcohol + sodium stearoyl lactylate
- polyglyceryl-2 isostearate (or resp. di/tri/tetra isostearate)
- polyglyceryl-3 diisostearate

6. Various other sugar-esters:
- Cetearylglucoside + Cetearyl alcohol
- methyl glucose sesquistearate + PEG-20 methyl glucose sesquistearate
- Sorbitan stearate + sucrose cocoate
- Sorbitan stearate + polysorbate 60
- sucrose esters (laurate/palmitate/stearate/oleate/isostearate)

7. **Lecithins and other Phospholipids:**
- lecithin

Propellants include propane, butane, isobutane, dimethyl ether, chlorofluoroalkanes, carbon dioxide, nitrous oxide.

Solvents include ethyl alcohol, methylene chloride, isopropanol, ethyl ethers such as ethoxyethanol and butoxyethanol, acetone, tetrahydrofuran, dimethyl formamide, DMSO, propylene glycol, butylene glycol.

Humectants include proteins and protein hydrolysates, amino acids, sorbitol, glycerin, sorbitol, glycols preferably PEG 200-4000 and other polyols.

Thickeners include cross linked polyacrylates, silicone gums and polysaccharide gums such as xanthan, carrageenan, gelatin, pection and locust beans gum, hyaluronic acid and carboxylic group-containing polymers

Powders include chalk, talc, starch, kaolin, clays, silicates, carboxyvinyl polymers.

Other active ingredients include:
- anti-oxidants like butyl hydroxy toluene, ascorbic acid and salts, EDTA, hydroquinone, tocopherols, gallates;
- preservatives like para-hydroxy benzoate esters, sorbic acid, EDTA, quaterniums, benzoic acid, imidazolidinyl urea, (benzyl)alcohol;
- enzyme regulators like vitamins and other co-factors;
- penetration enhancers like mono- or di-esters of C2 to C10 alcohols and C8 to C18 fatty acids, propanols, urea, sugar esters, POE esters or ethers of fatty acids and/or alcohols, butan-1,4 diol, tetrahydrofuran, salicylate salts, pyrrolidones, N-alkyl-aza-cycloheptanones, oleic acid, linoleic acid;
- sunscreens, blocking UV light, like PABA's, cinnamate and salicylate derivatives;
- other actives like coloring agents or perfumes.

The combination of the said components can account for 5 to 99% of the composition.

The positive and beneficial effects of the compositions according to the invention on affected skin

areas are various and are summarized as follows: a reduction of redness, dryness, roughness and/or scaling of the skin, a reduction of pruritis, a reduction of skin lesions, an improvement in healing of small wounds, a decrease of inflammatory symptoms in affected areas, a decrease of an infectious state of the skin in affected areas.

Examples of skin conditions which benefit from topical application of a composition according to the invention are psoriasis, atopic dermatitis, irritant and allergic contact dermatitis, seborrheic and sebostatic dermatitis, photodermatitis (UV-induced erythema), acne, ichthyosis, xerosis, aged skin. The skin infections which benefit from topical application of the compositions of the invention include bacterial, fungal, yeast and viral infections. For example dandruff, impetigo, Pityriasis vesicolor, Tinea corporis, Rosacea, Herpes, venereal diseases.

For specific skin conditions, i.e. wounds, burns, scalds, a combination of a free sphingoid base and a cerebroside is preferred, since cerebrosides (contrary to ceramides) tend to stimulate the proliferation of keratinocytes.

On the other hand, for skin diseases where, next to an impaired barrier function and skin infections, hyperproliferation, reduced differentation and reduced desquamation are general symptoms, the inclusion of ceramides with a short-chain acyl group may be advantageous. These short-chain ceramides will have the additional effect that they are cell-permeable and known to reduce proliferation, increase differentiation and increase desquamation.

The present invention is exemplified by several formulations and by an efficacy study using test persons with different skin disorders. Furthermore, the antiimflammatory activity of a free sphingoid base is demonstrated.

Example 1
Formulations comprising phytosphingosine and several ceramides

Below, several examples of suitable formulations according to the invention are given.
The ceramides and the free sphingoid base used in these formulations are the following:

Ceramide III: N-stearoyl-phytosphingosine
Ceramide IIIB: N-oleoyl-phytosphingosine
Ceramide VI: N-alpha-hydroxystearoyl-phytosphingosine
Phytosphingosine: 2-amino-octadecane-1,3,4-triol
Phytoceramide I: N-stearoyloxyheptacosanoyl-phytosphingosine

Waterless Barrier Cream I
comprising Ceramide III, Ceramide VI and Phytosphingosine

INCI-name	Trade name	Percentage (% w/w)
Hydrogenated lecithin		4.0
Glycerin		48.0
Butylene glycol		18.0
Jojoba oil		5.0
Propylene glycol dicaprylate/dicaprate	Miglyol 840 (Huls)	10.0
Isocetyl alcohol	Eutanol G16 (Henkel)	3.0
Tocopheryl acetate		5.0
Dimethicone copolyol eicosonate		5.0
Ceramide 3	Ceramide III (Cosmoferm) Ceramide IIIB (Cosmoferm)	0.5 0.5
Ceramide 6	Ceramide VI (Cosmoferm)	0.5
Phytosphingosine	Phytosphingosine (Cosmoferm)	0.5

Waterless Barrier Creams II and III

comprising Ceramide III, Ceramide VI and Phytosphingosine, and additionally cholesterol and stearic acid

INCI-name	Trade name	Percentage (% w/w)	
Hydrogenated Lecithin	Amisol 905 (Lucas Meyer)	4.0	4.0
Glycerin		30.0	24.0
Butylene glycol		20.0	20.0
Glycero phospholipids	Biophilic S (Lucas Meyer)	1.5	1.5
Jojoba oil		5.0	5.0
Paraffin		10.0	10.0
Propylene glycol dicaprylate/ dicaprate	Myritol PC (Henkel)	10.0	10.0
Isocetyl alcohol	Eutanol G16 (Henkel)	8.0	8.0
Hydrogenated vegetable oil	Cremeol HF52 (Aarhus)	5.0	5.0
Tocopheryl acetate	BASF	5.0	5.0
Ceramide 3	**Ceramide III (Cosmoferm)** **Ceramide IIIB (Cosmoferm)**	**0.25** **0.25**	**1.25** **1.25**
Ceramide 6	**Ceramide VI (Cosmoferm)**	**0.25**	**1.25**
Phytosphingosine	**Phytosphingosine (Cosmoferm)**	**0.25**	**1.25**
Cholesterol		**0.25**	**1.25**
Stearic acid	**Unichema**	**0.25**	**1.25**

Amisol 905 40% Hydrogenated lecithin, 30% Glycerin, 30% Butylene glycol.

Percentages have been corrected for glycerin and butylene glycol in the INCI-formulation

Barrier Cream IV

comprising Phytoceramide I, Ceramide III and IIIB, Ceramide VI, Phytosphingosine and Acetyl-phytosphingosine

INCI-name	Trade name	Percentage (% w/w)
Lecithin (and) C12-16 alcohols (and) palmitic acid	Biophilic S (Lucas Meyers)	2.0
Polyglyceryl-3 Methylglucose Distearate	Tego Care 450 (Goldschmidt)	2.0
Cetearyl alcohol	Lanette O (Henkel)	1.0
Propylene glycol dicaprylate/dicaprate	Myritol PC (Henkel)	10.0
Isocetyl alcohol	Eutanol G16 (Henkel)	10.0
Rice Bran oil		5.0
Tocopheryl acetate	BASF	2.0
Ceramide 3	**Ceramide III (Cosmoferm** **Ceramide IIIB (Cosmoferm)**	0.5 0.5
Ceramide 6	**Ceramide VI (Cosmoferm)**	0.5
Phytosphingosine	**Phytosphingosine (Cosmoferm)**	0.5
Ceramide 1	**Phytoceramide 1 (Cosmoferm)**	0.1
Acetyl-Phytosphingosine	**C2-Ceramide (Cosmoferm)**	0.1
Stearic acid		0.5
Cholesterol		0.5
Butylene glycol		6.0
Mixed parabens in Phenoxyethanol	Phenonip	0.6
Water		64.4

Liposomal formulation

comprising Ceramide III, Ceramide IIIB, Ceramide VI and phytosphingosine, and additionally cholesterol and linoleic acid

INCI-name	Trade name	Percentage (% w/w)
Sodium lauroyl lactylate		9.0
Tocopherol acetate		0.01
Carbomer		0.3
Ceramide 3	**Ceramide III (Cosmoferm** **Ceramide IIIB (Cosmoferm)**	**0.2** **0.2**
Ceramide 6	**Ceramide VI (Cosmoferm)**	**0.1**
Phytosphingosine	**Phytosphingosine (Cosmoferm)**	**0.5**
Linoleic acid		0.25
Cholesterol		0.25
Water		89.2

Example 2

Efficacy evaluation of barrier cream I

To test the efficacy of a composition comprising a free sphingoid base and a ceramide, barrier cream I was applied daily by several test persons suffering from various skin disorders. The results are indicated in Table 1. It is clear that the use of a barrier cream according to the invention results in a significant improvement of the affected skin areas.

Table 1

Person	Condition	Application	Effect
1	Psoriatic lesions on right leg	8 weeks 1* per day	Strong improvement; lesions have practically disappeared; small wounds appear to heal faster
2	Dry xerotic skin, in particular on cheeks	3 weeks 1* per day	Clear improvement; skin is less scaly and red
3	Ichtyosis over whole body	8 weeks 1* per day, only on the face	Improvement is visible; no itching feeling like with urea cream
4	Atopic skin	4 weeks 1* per day	Improvement; comparable to corticosteroid cream
5	Psoriatic lesions on the elbow	4 weeks 1* per day	Improvement; lesions return upon withdrawal

Example 3

Effect of the free sphingoid base phytosphingosine on the secretion of cytokines as a marker for antiinflammatory activity

Principle:

The effect of phytosphingosine was assessed *ex vivo* on excised human skin explants.

The explant was exposed to UV-B rays as a physical, proinflammatory stress.

The antiinflammatory effect of phytosphingosine was evaluated by measurement of the amount of the cytokine IL-1α secreted in the incubation medium of the skin explants.

Protocol:

- Preparation of the human skin explants obtained after plastic surgery using standard techniques.
- Application of the test product:
  resp. 0% (Placebo), 0.2 and 0.5% phytosphingosine (PS) in Propylene glycol : Ethanol (60:40).
  Dexamethasone (1 μM) was used as the reference product.

- The products were applied before and after irradiation (~2 mg/cm²)
- IL-1α secretion was measured in the incubation medium of the skin explants, using a standard ELISA technique.
- Each experimental condition was performed in triplicate.

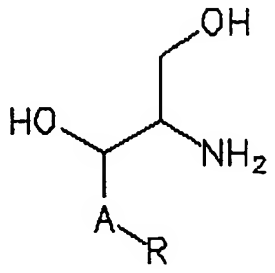
Results:

Before UV-B	After UV-B	Dexamethasone	Placebo	0.2% PS	0.5% PS
48	205	116*	165	82*	92*

* Significant effect $p < 0.05$
- Results are expressed in pg per ml IL-1α

Claims

1. A composition for topical use comprising a combination of a free sphingoid base and a ceramide, said free sphingoid base having a general structure according to Formula 1:



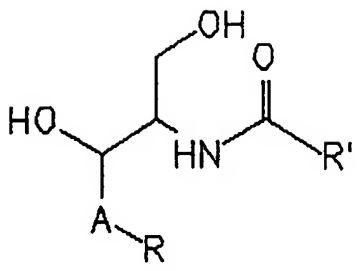
(1)

wherein:

A is CH_2-CH_2, CH=CH or C(H)OH-CH_2, and

R is a straight chain or branched alkyl group having 10 to 22 carbon atoms which may optionally contain one or more double bonds and/or may optionally be substituted with one or more hydroxyl groups, preferably is a straight chain alkyl group having 12 to 18 carbon atoms, more preferably is a straight chain alkyl group having 13 carbon atoms, and

said ceramide having a general structure according to Formula 2:



(2)

wherein:

A and R are defined as above, and

R' is a straight chain or branched alkyl group having 13 to 55 carbon atoms, preferably 15 to 50 carbon atoms, more preferably 17 to 44 carbon atoms; the alkyl chain may optionally be interrupted by an oxygen atom or by an internal ester group; may optionally contain one or more double bonds; and may optionally be substituted with one or more hydroxyl groups.

2. The composition of claim 1, wherein the free sphingoid base is selected from the group of sphingosine, sphinganine and phytosphingosine.

3. The composition of claim 1 or 2, wherein the ceramide is a ceramide which corresponds in stereochemical configuration to a ceramide isolatable from mammalian skin.

4. The composition of any one of the claims 1-3, wherein the ceramide is a mixture of two or more different ceramides.

5. The composition of any one of the claims 1-4, wherein the composition further comprises one or more additional skin lipid compounds.

6. The composition of any one of the claims 1-5, wherein a ceramide is present in addition to or instead of the ceramide according to Formula 2 which is selected from the group of glycoceramides and short chain ceramides.

7. The composition of claim 1 which is a dermatological composition.

8. The composition of claim 1 which is a cosmetic composition.

9. Use of the composition of claim 1 for the manufacture of a topical composition for the treatment of a skin condition associated with an impaired barrier function.

10. Use according to claim 9, wherein said skin condition is further associated with a condition selected from the group consisting of a deranged regulation of cell growth and differentiation, an imflammatory condition or an infectious state.

11. A method for the treatment of a skin condition associated with an impaired barrier function comprising the topical application of a composition according to claim 1.

12. The method of claim 11, wherein said skin condition is further associated with a condition selected from the group consisting of a deranged regulation of cell growth and differentiation, an imflammatory condition or an infectious state.

13. The method of claim 12 which is a non-therapeutical method.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/08121

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 16635 A (GIST-BROCADES) 6 June 1996 see claims 1,7-9,11-13	1,2,9-11
A	WO 97 09307 A (GIST-BROCADES) 13 March 1997 see claims	1,2
A	US 5 627 056 A (CASEY, J. ET AL.) 6 May 1997 see claim 1; examples	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 1999	19/04/1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 98/08121

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